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ISSUE HIGHLIGHTS

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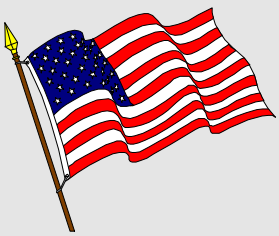
ARMED FORCES DAY
MEMORIAL DAY



REMEMBERING THE SACRIFICES

NSAIDs and Related Agents for Chronic Arthritic Conditions

The non-narcotic treatment of pain and inflammation usually involves the use of salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. NSAIDs and similar compounds are widely used for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), spondyloarthropathies, traumatic musculoskeletal pain from sports injuries or strained muscles, menstrual disorders, febrile states, and other nonspecific aches and pains.[1-4]

It is estimated that the Department of Defense spent over $30 million for NSAIDs in fiscal year 1993. Half of all consumption of NSAIDs is for the management of pain associated with OA,[5] thus this review primarily focuses on chronic therapy with NSAIDs and related agents. Ketorolac and mefenamic acid are not evaluated because these agents are indicated for only short-term relief of pain or dysmenorrhea.[1] Additionally, phenylbutazone is not included since it was discontinued by the distributor.[6] Other agents not considered in this evaluation due to limited use are magnesium salicylate, sodium salicylate, and choline salicylate. Magnesium salicylate may cause hypermagnesemia in patients with compromised renal function.[3] Sodium salicylate is seldom used because of patient intolerance and the sodium content of the drug, and choline salicylate is available only as a liquid formulation because it is too hygroscopic for a solid dosage form.[7]

Pharmacoeconomic Analysis

A pharmacoeconomic analysis of the NSAIDs and salicylate compounds for chronic arthritic conditions must take into account all reasonable costs of therapy over a given period of time, including the probabilities of treatment failure and adverse reactions and their associated costs. Comparative trials have shown little difference in efficacy among the NSAIDs.[5,8,9] Additionally, controlled clinical trials comparing NSAIDs to aspirin found no

significant difference in efficacy.[8] Because the efficacy of these drugs, in general, is similar, adverse effects of the drugs become a major differentiating factor. The incidence of major adverse reactions associated with most NSAIDs has been evaluated by the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) Post-Marketing Surveillance Program.[10] However, the hospital admission rates for various specific complications have not been reported.[10-12] Hospitalizations associated with complications add to the cost of treatment and must be included in any valid pharmacoeconomic analysis. The ARAMIS database will eventually provide this information, and the PEC will follow up with a full analysis as these data become available.

Interim Recommendations

These guidelines for NSAID and salicylate prescribing are provided to assist providers in selecting the safest, most efficacious treatments for their patients to alleviate pain and disability due to arthritis or other painful musculoskeletal disorders at an optimal cost.

- *Nonpharmacologic treatments should be implemented, when possible, prior to or in conjunction with, pharmacologic therapy.*[13,14] Rehabilitative therapy and patient education are important components in the treatment of OA and RA. Weight loss, the use of canes or other assistive devices, isometric and low-impact aerobic exercise programs, and alternating warm/cold soaks can be symptomatically helpful for OA patients.[14,15] Patients with RA can benefit from joint rest or splinting, muscle strengthening exercises, and various assistive devices.[16] Nonpharmacologic measures are also appropriate for strains, sprains, and other sports injuries.

- *For non-inflammatory conditions, acetaminophen should be considered for initial pharmacologic therapy.* Although acetaminophen lacks anti-inflammatory effects, its antipyretic and analgesic effects are comparable to those of aspirin.[4] Clinical trials have not demonstrated the superiority of NSAIDs over acetaminophen in OA.[17,18] These data support the use of simple analgesics, like acetaminophen, for chronic, non-inflammatory causes of pain, such as OA. A 2 to 3 week trial of acetaminophen should be the initial pharmacologic intervention for these conditions. Discomfort associated with acute, self-limited musculoskeletal pain, menstrual cramps, or fever can be self-treated with intermittent doses of acetaminophen until the condition resolves spontaneously. Analgesic doses of ibuprofen or aspirin can also be used for these conditions.[5,19] NSAIDs should be reserved for conditions associated with a significant inflammatory component.

- *If anti-inflammatory properties are essential to maintain an acceptable quality of life for a patient, enteric-coated aspirin, ibuprofen, or nonacetylated salicylates, such as choline/magnesium salicylate or salsalate, should be used initially.*[13] Clinical trials have shown equal efficacy between aspirin and nonacetylated salicylates,[20,21] and aspirin and NSAIDs.[8] If these first-tier agents are not effective, the NSAID with the lowest acquisition cost and the lowest relative toxicity should be initiated[13] (Table 1).

- *Start NSAIDs or salicylates at low doses, if feasible, and increase the daily dose every 2 to 3 weeks as necessary to control symptoms.* Although comparative trials have shown little difference in efficacy among the NSAIDs,[5,8,9] significant interpatient variability has been demonstrated.[5,9] Currently, no method is available to predict which NSAID will be most effective in an individual patient. Comorbid illnesses, such as peptic ulcer disease, congestive heart failure, or renal or hepatic insufficiency, and concurrent drug therapy must be considered when selecting a NSAID.[19,22] Use the lowest effective dosage with periodic trials of discontinuation to reassess efficacy.[13] RA patients may require the maximum dose of a NSAID for adequate symptom relief. NSAIDs with a long half-life can be dosed once or twice daily to optimize patient compliance[19] (Table 2).

Table 1. Relative Ranking of NSAIDs and Related Compounds by Toxicity Score

Drug	Toxicity Index Score*	Drug Acquisition Cost/ Year at Maximum Dose†
First-Tier Agents		
Acetaminophen	‡	$14.60
Salsalate	1.79	$59.86
Ibuprofen	1.95	$32.12
Aspirin (enteric-coated)	2.25	$13.14
Choline/Magnesium Salicylate	‡	$73.00
Second-Tier Agents		
Naproxen	3.29	$91.98
Diclofenac sodium	3.54	$675.98
Ketoprofen (immediate-release)	3.74	$223.38
Tolmetin	3.77	$306.60
Piroxicam	3.83	$33.58
Fenoprofen	3.96	$516.84
Sulindac	3.98	$116.80
Third-Tier Agents		
Indomethacin (immediate-release)	5.14	$27.74
Meclofenamate	5.40	$181.04
Fourth-Tier Agents		
Diflunisal	‡	$632.91
Etodolac	‡	$482.89
Flurbiprofen	‡	$383.25
Oxaprozin	‡	$470.85
Nabumetone	‡	$759.20

* Toxicity Index Scores were calculated from patient adverse effects, laboratory abnormalities, and hospitalizations. The scores were standardized to adjust for covariant. Mean scores are reported with a range from 1-6. A score of 1 represents lowest risk of toxicity, and a score of 6 represents the highest risk of toxicity. See References 10-12 for additional detail.

† Drug acquisition cost is calculated from maximum daily dose of drug and best price available to DOD

‡ Toxicity Index Scores are not available for this drug. Rankings for acetaminophen and choline/magnesium salicylate are based on relative toxicity compared with other salicylate compounds.

- *Allow at least 2 weeks for the anti-inflammatory effect of a NSAID to be established before assessing its efficacy.* The initial supply of medication dispensed to the patient should be limited to an amount that will reduce wastage if the drug is ineffective or not well tolerated. Larger quantities should be dispensed once an effective and well-tolerated agent is found.[13]

- *If one NSAID or salicylate is not effective, others may be tried in sequence considering acquisition cost and relative toxicity* (Table 1). If a trial of several NSAIDs fails to find one that is substantially better than the others, use the least expensive drug that was well tolerated.[13] The benefit of using a marginally effective NSAID must be weighed against the risk of potential drug toxicities. Efficacy studies suggest that 50% of patients will respond to the first NSAID prescribed. A further 30% will respond to a second (alternative) NSAID, and 7% remain dissatisfied after 4 or more agents.[23]

- *Do not use more than one NSAID at a time. Do not combine a NSAID and aspirin.* No additional efficacy benefit is obtained with combinations of NSAIDs or aspirin. Additionally, combination therapy increases the risk of GI adverse effects.[13]
- *For patients at risk for GI adverse effects who require NSAIDs, a drug with a short-half is preferable to one with a long-half life that inhibits platelet aggregation for a prolonged period*[19] (Tables 2 and 3). GI adverse effects

occur in approximately 25% of patients who use NSAIDs, including salicylates. Treatment of these GI effects accounted for 31% of the total cost of arthritis care.[24] Patients using these agents have an increased risk of peptic ulceration and GI bleeding.[13] In general, the NSAIDs have a 2% to 4% incidence of peptic ulceration; however, nabumetone is an exception with a cumulative incidence of peptic ulceration of 0.3% at 3 to 6 months, 0.5% at 1 year, and 0.8% at 2 years.[25]

These GI complications are more common in the elderly,[13] and patients older than 60 years are 3 times more likely to die because of these complications than those under 60 years of age.[26] The GI toxicity of NSAIDs is both dose and duration dependent. Retrospective reviews of Medicaid data demonstrated a linear dose-response relationship between upper GI bleeding and NSAID dose.[13]

- *Prophylaxis against NSAID-induced upper GI effects with misoprostol should be reserved for patients who need to continue anti-inflammatory therapy, but are at high risk for GI complications*[13] (Table 3). Scoring systems are available to calculate the risk of serious GI complications.[22,26] Misoprostol is effective in preventing and healing NSAID-induced gastric ulceration even when NSAID therapy is continued. Additionally, misoprostol appears to improve NSAID-induced duodenal ulcers.[26] Although misoprostol is effective in preventing gastroduodenal ulceration, adverse effects caused by the drug are a major limiting factor to its use.

Table 2. Pharmacokinetics and Dosing Parameters for NSAIDs and Related Agents[1-4,25]

Generic Name (Brand Name)	Time to Peak Conc. (hrs)	Half-life (hrs)	Maximum Dose/Day (mg)*	Dosage Interval
Acetaminophen†	0.5-2	1-4	4000 (short-term) 2600 (long-term)	TID-QID
Aspirin†	1-2	5-18	6000§	BID-QID
Choline/Mg Salicylate (Trilisate®)	1-2	9-17	3000§	QD-TID
Diclofenac (Voltaren®)	1-4	1-2	200	BID-QID
Diflunisal (Dolobid®)†	2-3	8-12	1500	BID
Etodolac (Lodine®)	1-3	6.5-7.3	1200	BID-QID
Fenoprofen (Nalfon®)†	1-2	2-3	3200	TID-QID
Flurbiprofen (Ansaid®)	1.5	5.7	300	BID-QID
Ibuprofen (Motrin®)†	1-2	1.8-2.5	3200	TID-QID
Indomethacin (Indocin®)†	1-2 SR: 2-4	4.5 SR: 4.5-6	200 SR: 150	BID-TID SR: QD-BID
Ketoprofen (Orudis®)†	0.5-2 SR: 6-9	2-4 SR: 5.4	300 SR: 200	TID-QID SR: QD
Meclofenamate (Meclomen®)†	0.5-2	0.8-3.3	400	TID-QID
Nabumetone (Relafen®)	2.5-4	22.5-30	2000	QD-BID
Naproxen (Naprosyn®)†	2-4	12-13	1250 1500 (short-term)	BID
Naproxen sodium (Anaprox®)†	1-2	12-13	1375 1650 (short-term)	BID
Oxaprozin (Daypro®)	3-5	42-50	1800	QD-TID
Piroxicam (Feldene®)†	3-5	30-86	20	QD-BID
Salsalate (Disalcid®)†	1-2	5-18	3000§	BID-TID
Sulindac (Clinoril®)†	2-4	7.8-16.4	400	BID
Tolmetin (Tolectin®)	0.5-1	1-5	1800	TID-QID

* Maximum dose per day as indicated for osteoarthritis or rheumatoid arthritis. Doses may vary from patient to patient.
† Generic products are available for these drugs. Brand names are provided for example only.
§ Maximum dose is titrated to salicylate level of 15-30 mg/dL.

Diarrhea, the most frequent adverse effect, occurs in up to 40% of patients taking the recommended dose of 200 μg four times a day.[25,26] With a reduced dose of 100 μg four times a day, up to 25% of patients will develop diarrhea.[26] The lower dose of misoprostol is somewhat less effective than the recommended dose.[25] Although histamine H_2-receptor antagonists (H_2RAs) and sucralfate are effective in healing NSAID-induced ulceration when NSAID therapy is discontinued,[5] these agents may be ineffective in reducing the incidence of gastroduodenal ulceration.[22] The ARAMIS data suggest H_2RAs and sucralfate are not efficacious in preventing serious GI events since the rate of these events is actually higher in patients using these agents.[22]

Table 3.
Risk Factors for NSAID GI Toxicity[13,22]

Prior peptic ulcer disease
Age > 60 years
Prior NSAID intolerance
Corticosteroid use
High NSAID dose
Cigarette smoking
Degree of disability

- *For patients at mild to moderate risk of reversible renal failure with NSAID use, acetaminophen or nonacetylated salicylates are the potentially the least toxic. For patients at high risk, all salicylates and all NSAIDs should be avoided.* Risk factors for NSAID nephrotoxicity include patients with intrinsic renal disease, hepatic cirrhosis, congestive heart failure, diuretic use, and the elderly. These patients are more likely to be dependent on local prostaglandin synthesis for maintenance of renal blood flow and glomerular filtration, thus inhibition of renal cyclooxygenase in these settings can lead to acute renal failure.[13] Chronic acetaminophen and NSAID usage, but not aspirin usage, have been reported to have an increased association with end stage renal disease.[27] Patients with gout should avoid salicylates since they may increase serum uric acid which can precipitate or prolong an attack.[3]

- *Hepatic toxicity has been reported with all NSAIDs, but acetaminophen, diclofenac, and sulindac appear to have the highest incidence.*[9,19] *Ibuprofen, indomethacin, naproxen, and ketoprofen appear to have the lowest incidence of these effects.*[9] Elevations of more than one liver function test in clinical trials in RA patients have been observed in 5.4% of patients taking aspirin and 2.9% of patients taking other NSAIDs.[19] The potential for hepatotoxicity with acetaminophen is greatest at doses of greater than 4 gm/day, particularly in the presence of chronic alcohol use, hepatic dysfunction, or drugs that induce hepatic microsomal enzymes (e.g., phenobarbital, phenytoin, carbamazepine, and rifampin). To avoid potential hepatotoxicity, the dosage for long-term acetaminophen therapy should not exceed 2.6 gm/day without monitoring.[4]

- *Patients on anticoagulants requiring long-term analgesic therapy should use acetaminophen or nonacetylated salicylates before considering a NSAID.*[3,4] Patients receiving concomitant warfarin and NSAIDs or salicylates require careful monitoring and adjustments of warfarin dosage because of potentially prolonged prothrombin times.[1,19] Inhibition of platelet function is an important hematologic effect that may aggravate gastrointestinal hemorrhage. Aspirin irreversibly inhibits platelet function, but NSAIDs reversibly impair platelet function.[9] The nonacetylated salicylates appear to have no significant effect on platelets[9.19] and acetaminophen has no platelet inhibition.[4] When NSAIDs are necessary, those with short half-lives should be used to minimize the duration of antiplatelet effects.[9]

- *Patients should be assessed every 2 to 3 months during the first year of chronic NSAID, acetaminophen, or salicylate therapy.* This assessment is particularly important for patients at increased risk of NSAID-induced toxicity. A general assessment should consist of a patient history with an emphasis on patient response to

therapy and adverse effects, physical examination, laboratory tests, such as hematocrit, blood urea nitrogen, serum creatinine, and urinalysis.[2] Liver function tests are recommended within the first 8 weeks of therapy for patients taking diclofenac[25]; liver function tests for other NSAIDs are recommended periodically.[2,4] Additionally, patients may be screened for occult blood in the stool; however, the optimal method and frequency of screening are not known.[2] Salicylate therapy also can be monitored by serum salicylate concentrations. The therapeutic range for salicylate therapy is 15 to 30 mg/dL.[3]

Summary

The recommendations in this Update provide general guidance to practitioners for cost-effective NSAIDs prescribing. The PEC is developing a pharmacoeconomic model to evaluate the NSAIDs and salicylate compounds for the treatment of chronic arthritic conditions. However, the data for hospital admissions due to complications of these drugs are not complete. When these data are available, the PEC will complete the analysis and recommend changes, if any, to the Tri-Service Formulary.

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